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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

JACOTOT ET AL. Atty. Ref.: 1721-112

Serial No. 10/573,576 Group: Unknown

Filed: March 24, 2006 Examiner: Unknown

For: PEPTIDES HAVING, FOR EXAMPLE, ANTIANGIOGENIC ACTIVITY AND APPLICATIONS THEREOF IN THERAPEUTICS

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August 24, 2006

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1540

Sir:

SUBMISSION

Submitted herewith is a copy of the English translation of the International Preliminary Examination Report issued in the corresponding PCT/FR2004/002422.

Respectfully submitted,

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PATENT COOPERATION TREATY

Translation

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	See form PCT/ISA/210
Applicant's or agent's file reference 61114	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/FR2004/002422	24.09.2004	25.09.2003

International Patent Classification (IPC) or both national classification and IPC
A61K38/00, C07K14/00, A61P35/00

Applicant
THERAPTOSIS

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/EP	Authorized officer
Facsimile No.	Telephone No.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/FR2004/002422

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rule 12.3 and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☒ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☒ in written format

☒ in computer readable form

c. time of filing/furnishing

☒ contained in the international application as filed.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/FR2004/002422

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-12	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-12	NO
Industrial applicability (IA)	Claims	1-12	YES
	Claims		NO

2. Citations and explanations:

Reference is made to the following documents in the present notification:

D1: KAWAGUCHI MICHIYA ET AL: "A novel synthetic Arg-Gly-Asp-containing peptide cyclo(-RGDfdbdV-) is the potent inhibitor of angiogenesis" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 288, no. 3, 2 November 2001 (2001-11-02), pages 711-717,

D2: KUMAR C CHANDRA: "Integrin alphavbeta3 as a therapeutic target for blocking tumor-induced angiogenesis." CURRENT DRUG TARGETS, vol. 4, no. 2, February 2003 (2003-02), pages 123-131,

D3: WESTLIN W F: "Integrins as targets of angiogenesis inhibition." CANCER JOURNAL (SUDBURY, MASS.) 2001 NOV-DEC, vol. 7, Suppl 3, November 2001 (2001-11), pages S139-S143,

D4: WO 00/49038 A (SCHUBERT, ULRICH; HENKLEIN, PETER; WRAY, VICTOR) 24 August 2000 (2000-08-24),

D5: RUEGG C ET AL: "Vascular integrins: Pleiotropic adhesion and signaling molecules in vascular homeostasis and angiogenesis." CMLS CELLULAR AND MOLECULAR LIFE SCIENCES, vol. 60, no. 6, June 2003, p 1135-1157,

D6: CONSTANTINI P ET AL: "Mitochondrion as a novel target of anticancer chemotherapy." JOURNAL OF THE NATIONAL CANCER INSTITUTE. 5 JUL 2000, vol. 92, no. 13, 5 July 2000 (2000-07-05), pages 1042-1053,

D7: SCHRAA ASTRID J ET AL: "Endothelial cells internalize and degrade RGD-modified proteins developed for tumor vasculature targeting." JOURNAL OF CONTROLLED RELEASE:

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

OFFICIAL JOURNAL OF THE CONTROLLED RELEASE SOCIETY. vol. 83, no. 2, 4 October 2002, pages 241-251,

D8: HAUBNER R ET AL: "STEREOISOMERIC PEPTIDE LIBRARIES AND PEPTIDOMIMETICS FOR DESIGNING SELECTIVE INHIBITORS OF THE ALPHAVBETA3 INTEGRIN FOR A NEW CANCER THERAPY" ANGEWANDTE CHEMIE. INTERNATIONAL EDITION, VERLAG CHEMIE. WEINHEIM, DE, vol. 36, 1997, pages 1375-1389,

1 Novelty (PCT Article 33(2))

The present application complies with the requirements of PCT Article 33(1) since the subject matter of claims 1-12 meets the requirement of novelty defined in PCT Article 33(2). None of the documents of the prior art describes the cyclized peptides claimed (and also the uses thereof).

2 Inventive step (PCT Article 33(3))

2.1 The present application fails to comply with the requirements of PCT Article 33(1) since the subject matter of claim 1 does not involve an inventive step as defined in PCT Article 33(3).

2.1.1 Document D1, which is considered to be the prior art closest to the subject matter of claim 1, describes peptides containing (RGD) motifs which are ligands for $\alpha_v\beta_3$ integrin and which act as angiogenic inhibitors. In D1, a novel cyclic RGD peptide cyclo(-RGDf=V-)(f=V) was synthesized so as to test its biological activity with the analogues cyclo(-RGDfV-) and cyclo(-RGDf-MeV-) (fMeV). The results demonstrate the potential and the advantage of the cyclic RGD peptides for use as anti-angiogenic agents (document D7 comes to the same conclusion with -RGD- peptides).

2.1.2 Therefore, the subject matter of claims 1 differs from the teachings of D1 in that the sequence SEQ ID No.1 is not disclosed as such.

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

2.1.3 The problem that the present invention is intended to solve can thus be considered to be that of the provision of alternative cyclized peptides containing an RGD motif and having anti-angiogenic activity.

2.1.4 The solution, as proposed in claim 1 of the present application, is not considered to be inventive (PCT Article 33(3)) for the following reasons:
D2 recalls that the integrin receptor plays an important role in various processes such as tumoral angiogenesis or metastasis. This was proved by the use of $\alpha_v\beta_3$ antagonists such as antibodies or small compounds capable of blocking angiogenesis and tumour growth in animal models. Thus, D2 considers that the $\alpha_v\beta_3$ receptor is an important target for pharmacological applications.

Similarly, D3 and D8 conclude that the inhibition of $\alpha_v\beta_3$ makes it possible to modulate the angiogenesis induced by tumour growth and would constitute a strategy for anti-cancer therapy.

D4 describes synthetic peptides derived from regulatory protein R of HIV-1 (Vpr). Certain peptides exhibit a structural similarity (based on the presence of the RGD motif) with the peptides of the present invention.

D5 discusses the role of integrins in endothelial cell functions and angiogenesis and their importance as therapeutic targets for the suppression of angiogenesis associated with cancerous tumours (e.g. $\alpha_v\beta_3$ integrin antagonists).

2.1.5 In view of the large number of peptide compounds covered by claim 1, it is not clear which structural motif is determinant for obtaining a biological effect (i.e. anti-angiogenic activity - moreover, neither is it certain whether the majority of the peptides of claim 1 possess

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

such an activity). In this sense, a person skilled in the art, starting from the features of documents D1 and D2 (cyclization of RGD peptides and $\alpha_v\beta_3$ antagonists for blocking angiogenesis and tumour growth) combined with the teaching of D3-D5, and from his knowledge of peptide chemistry, could, without showing an inventive mind, achieve the solution proposed in order to solve the problem stated. Therefore, the solution, as proposed in claims 1-8 (peptides), 9-10 (compositions) and 11-12 (medical use), thus cannot be considered to involve an inventive step (PCT Article 33(3)).